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FULL PAPER

Imaging features of primary and metastatic alveolar soft part sarcoma: single institute experience in 25 patients

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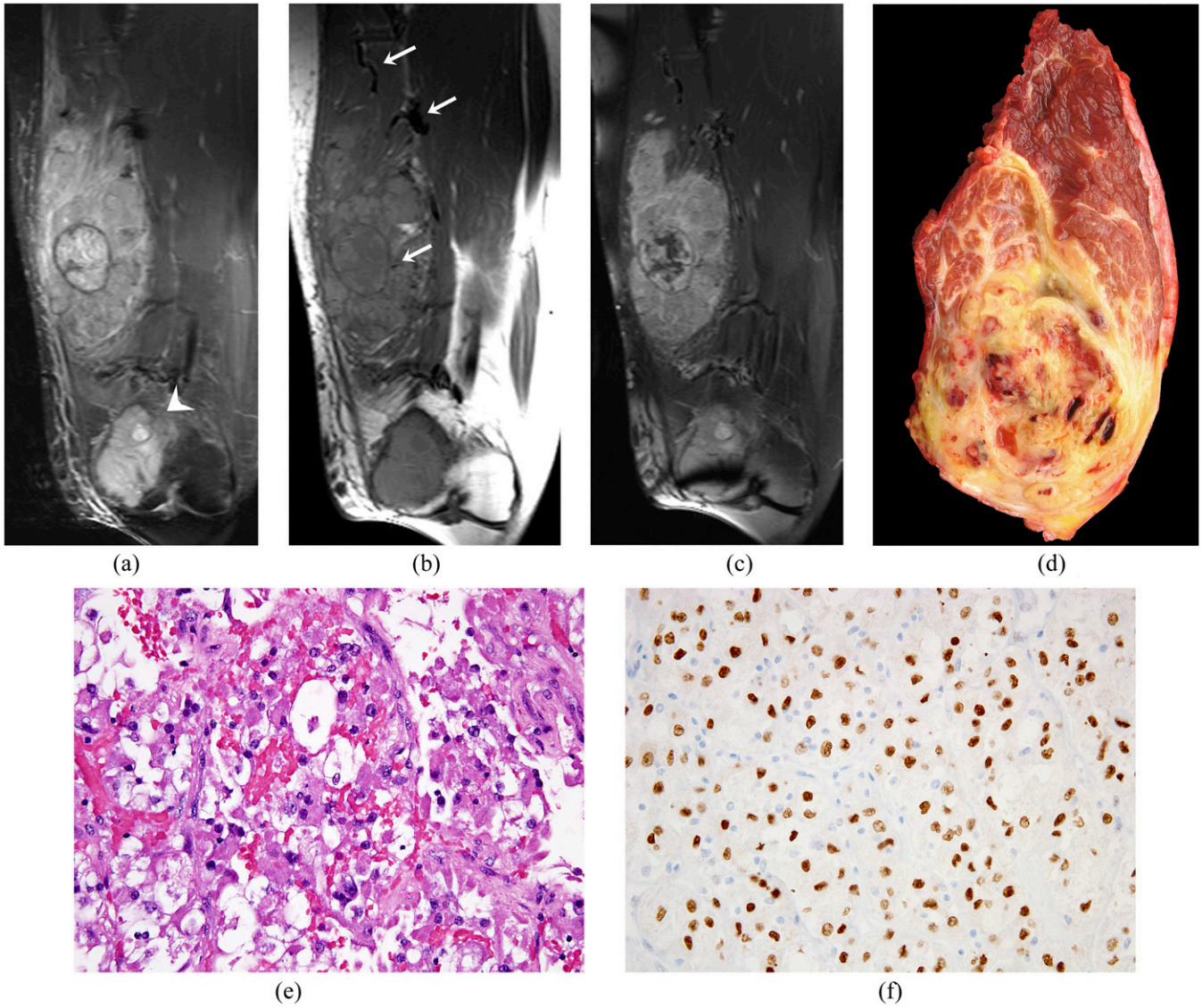
Objective: To describe imaging features of primary and metastatic alveolar soft part sarcoma (ASPS).
Methods: In this institutional review board-approved and Health Insurance Portability and Accountability Act-compliant retrospective study, 25 patients (14 males; mean age, 25 years; range, 18–40 years) with pathologically proven ASPS seen at our institute between 1995 and 2013 were included. Imaging of primary tumours in 5 patients and follow-up imaging in 25 patients were reviewed by 2 radiologists in consensus. Clinical information was obtained from electronic medical records.
Results: The most common sites for the primary tumour were extremities (17/25, 68%) and torso (6/25, 24%). Primary tumours ($n = 5$) were well circumscribed, compared with skeletal muscle, were isodense on CT, hyperintense on T_1 and T_2 weighted images with intense post-contrast enhancement, prominent feeders on CT and flow voids on MRI. Metastases developed in 23/25 (92%) patients, 18 at presentation. The most common sites of metastases were the lungs (100%), lymph nodes (74%), bones (57%) and brain (43%). Visceral and nodal metastases were hypervascular. At the time of reporting the results, 15 patients have died, 6 are alive and 4 were lost to follow-up. Median survival was 74 months for those without brain metastases ($n = 8$) and 60 months for those with brain metastases ($n = 7$). Median survival was shorter for patients with metastases at presentation.
Conclusion: ASPS most commonly involves the lower extremities of young adults, is hypervascular on imaging, often metastasizes at presentation, frequently to lung, nodes, bones and brain, and has an indolent course despite metastases. Brain metastases and high tumour burden (number of metastatic sites) at presentation decreased survival in our study.
Advances in knowledge: ASPS has an unusual pattern of metastases to the brain and nodes in addition to lung and bones. It has an indolent course despite metastases.

Alveolar soft part sarcoma (ASPS) is a rare type of sarcoma that accounts for approximately 0.5–1.0% of all soft-tissue sarcomas and predominantly affects children and young adults.[1,2] Histopathologically, ASPS is composed of large epithelioid tumour cells with abundant cytoplasm, arranged in nests or a pseudoalveolar growth pattern, surrounded by delicate sinusoidal vascular channels[3,4] (Figure 1). At a molecular level, ASPS is characterized by the unbalanced translocation t(X; 17)(p11; q25), which results in fusion of the transcription enhancer factor 3 (*TFE3*) gene at Xp11 to the *ASPSCR1* gene on chromosome 17 to create the ASPSCR1–TFE3 fusion protein[5–7] (Figure 1). Strong expression of TFE3 occurs almost exclusively in ASPS and in Xp11 translocation-associated paediatric renal cell cancers.[8]

In spite of the advances in the understanding of its pathogenesis, the origin of ASPS remains obscure. ASPS is resistant to conventional chemotherapy, with complete excision of the primary tumour and metastatectomy being the only proven modalities of treatment.[1,9] ASPS however is a slow-growing tumour that follows a relatively indolent course in spite of frequent metastases at the time of presentation.[10] It also has an unusual pattern of metastatic spread for a sarcoma, with the brain being a common site of metastases.[1]

While the radiological characteristics of primary ASPS have been described in the literature,[11,12] imaging features of its metastatic pattern with respect to distribution and morphology are not widely reported. The purpose of our study

Figure 1. Images of a 29-year-old male with alveolar soft part sarcoma (ASPS) of the right thigh. (a–c) Coronal short tau inversion–recovery, pre- and post-gadolinium T_1 weighted fat-suppressed MR images reveal a heterogeneous T_1 and T_2 hyperintense (relative to the adjacent muscles) mass involving the extensor compartment of the thigh in relation to the vastus lateralis with intense post-gadolinium enhancement. Note the prominent feeder vessels and flow voids (arrows, b). A metastatic lesion involving the distal femur is also visualized (arrowhead, a). Both the lesions were resected. (d) Gross resected specimen of the thigh sarcoma shows extensive necrosis. (e) On histopathology, there is a nested architecture, with the tumour being composed of large epithelioid cells with voluminous cytoplasm. (f) By immunohistochemistry, the tumour cells show strong nuclear staining for TFE3, reflecting the presence of a t(X; 17) translocation with the ASPSCR1–TFE3 fusion.



was to describe the imaging features of ASPS with emphasis on the metastatic pattern.

MATERIALS AND METHODS

Subjects

In this Health Insurance Portability and Accountability Act-compliant retrospective study approved by the institutional review board with waiver for informed consent, we identified 28 patients with histopathology-proven ASPS from the pathology database of our tertiary cancer institute. All these patients were treated at our bone and sarcoma specialist centre between 1995 and 2013. Three of them did not have imaging studies in our picture archiving and communication system (PACS) database and were excluded from the study. We reviewed the electronic medical records and imaging of the remaining 25 patients (14 males, 11 females; mean age, 25 years; range, 18–40 years). The histopathology of all patients was reviewed by an experienced histopathologist with special expertise in sarcomas to confirm the diagnosis of ASPS.

Imaging

Pre-treatment imaging of the primary tumour was available for 5/25 patients [22 CTs, 7 MRIs and 1 positron emission tomography (PET)/CT]. Follow-up imaging was available in all the

25 patients (157 CTs, 50 MRIs and 21 PET/CTs). Angiography was not performed on any patient. Multidetector CT (MDCT) images were acquired on 4-slice (GE Healthcare, Barrington, IL), 16-slice (Siemens Medical Solutions, Forchheim, Germany) and 64-slice MDCT (Aquilion™ 64; Toshiba America Medical Systems, Tustin, CA) scanners, with 5-mm-thickness axial images and 4-mm coronal reconstructions. Iopromide (300 mg I ml^{-1}; Ultravist® 300; Bayer Healthcare Pharmaceuticals, San Francisco, CA) was administered as intravenous contrast using an automated injector (Stellant®; Medrad®, Warrendale, PA) at a rate of 2–3 ml s^{-1}, with a scan delay of 60 s. The images were reviewed on a Centricity® PACS RA1000 (GE Healthcare) workstation. PET was performed from the base of the skull through the thighs (Discovery LS; GE Healthcare, Waukesha, WI, or Biograph™ 16-HiRes; Siemens Medical Solutions), with non-contrast helical CT imaging (5-mm-thickness axial images) performed over the same range without breath-hold for attenuation correction of PET images and anatomical correlation. The PET/CT images were reviewed on a HERMES GOLD™ (Hermes Medical Solutions Inc., Greenville, NC) workstation. The MRI examinations were performed on a 1.5-T MRI (GE Healthcare) or 3-T MRI (Siemens Medical Solutions) scanner with gadolinium administration at doses of 0.1 mmol kg^{-1} body weight up to a maximum dose of 20 ml. Primary tumour locations were grouped into "torso" (including the pelvic and shoulder girdles), "extremity" and "head-face-neck".

Clinical data and image analysis

The following clinical information was extracted from the electronic medical records: demographic data, date of diagnosis of primary tumour, date of diagnosis of metastasis, management of the primary tumour and metastases, duration of follow-up and outcome.

A systematic review of all the imaging studies was performed by two oncoradiology fellowship-trained radiologists with 5 and 8 years of experience in consensus. Imaging features of the primary tumour that were recorded included location, largest dimension, CT attenuation, T_1 and T_2 weighted signal intensities on MRI compared with skeletal muscle, enhancement characteristics on CT and MRI, the presence of heterogeneity, calcification and necrosis. On follow-up imaging, the presence, site, number (whether single or multiple) and imaging features of metastases were noted. Metastatic lesions were confirmed either at histopathology or by the presence of unequivocal progression on serial follow-up imaging. On PET/CT, the maximum standardized uptake values (SUVmax) of the primary and metastatic lesions were recorded. Statistical analysis was not performed because of the small number of patients.

RESULTS

The most common site of the primary tumour was the extremity (17/25 patients, 68%), with the lower extremity being involved in 16/17 (64%) and the upper extremity in 1/17 patients. The torso was involved in 6/25 patients (24%); pelvic/shoulder girdle in 5 patients; and the paraspinal region in 1 patient. Retro-ocular disease was noted in 1/25 patients, whereas the site of the primary tumour was unknown in 1/25 patients.

Imaging of primary alveolar soft part sarcoma

Imaging of the primary tumour was available in 5/25 patients (Table 1). The mean size of the primary tumour was 10.2 cm (range, 4.6–15.5 cm). On CT ($n = 5$), the primary tumours had well-defined margins and were isodense compared with the adjacent muscles on the non-contrast images. On MRI ($n = 3$), the primary tumours were hyperintense on T_2 and T_1 weighted images when compared with the adjacent muscles. All the tumours showed intense post-contrast enhancement on both CT and MRI with feeder vessels seen on CT and prominent flow voids seen on MRI consistent with marked hypervascularity (Figure 1). Tumours < 10 cm in size ($n = 2$) showed predominantly homogeneous post-contrast enhancement, whereas tumours > 10 cm in size ($n = 3$) showed heterogeneous peripheral enhancement with a central hypoenhancing component consistent with necrosis. One of the tumours involving the right thigh measuring 15.5 cm in size had specks of calcification within it. PET/CT was performed in

Table 1. Imaging characteristics of primary alveolar soft part sarcoma

Serial number	Site	Size (cm)	Margin	Outline	Flow void/ feeder vessels	Contrast enhancement	SI on T1W	SI on T2W
1	Retro-ocular	4.6	Relatively well circumscribed	Lobulated	+	Homogeneous	HI	HI
2	Thigh	10.0	Ill defined	Irregular	+	Heterogeneous peripheral enhancement	–	–
3	Thigh	9.5	Well circumscribed	Mildly undulating	+	Homogeneous	HI	HI
4	Gluteal	11.5	Relatively well circumscribed	Lobulated	+	Heterogeneous peripheral enhancement	–	–
5	Thigh	15.5	Ill defined	Irregular	+	Heterogeneous peripheral enhancement	HI	HI

HI, hyperintense; SI, signal intensity; T1W, T_1 weighted imaging; T2W, T_2 weighted imaging.

Table 2. Metastatic pattern in alveolar soft part sarcoma (23 patients)

Pulmonary metastases	23/23	
	Multiple bilateral	22
	Solitary	1
	Largest diameter at presentation	Mean, 3.6 cm
		Range, 0.9–11.3 cm
Nodal metastases	17/23	
	Intrathoracic	16
	Inguinal (locoregional)	4
	Pelvic	3
	Intra-abdominal	2
	Supraclavicular	3
Bony metastases	13/23	
	Solitary *vs* multiple	8 *vs* 5
	Lytic	11
	Sclerotic	1
	Mixed lytic and sclerotic	1
Brain metastases	10/23	
	Solitary *vs* multiple	4 *vs* 6
	Intra-axial	9
	Extra-axial	2
	Perilesional oedema	4
	Haemorrhagic	2
Liver	8/23	
Adrenal	8/23	
Subcutaneous	6/23	
Peritoneum	5/23	
Pancreas	3/23	

one patient, demonstrating moderate fludeoxyglucose (FDG) avidity with an SUVmax of 10.1.

Imaging of recurrent/metastatic disease

Follow-up imaging was available in all 25 patients. Local tumour recurrence developed in 2/25 patients on follow-up. The imaging features of recurrent disease were similar to those of the primary tumour. PET/CT was performed in both patients with local recurrence, which showed variable FDG uptake (SUVmax of 7.3 and 3.6, respectively).

Distant metastases developed in 23/25 patients, 18 of them being present at the time of presentation. Table 2 depicts the sites and frequency of metastatic disease. The lung was the most common site of metastases (23/23), followed by the lymph nodes in 17/23 (70%), bones in 13/23 (57%), brain in 10/23 (43%), liver in 8/23 (35%) and adrenals in 8/23 (35%).

In patients with lung metastases, multiple bilateral pulmonary nodules/masses were present in 22/23 patients (96%), and a solitary pulmonary nodule (4%) in 1 patient. None of the nodules showed cavitation. Other forms of neoplastic pulmonary involvement such as consolidation or lymphangitic spread were not observed. The mean largest diameter of the pulmonary metastases was 3.6 cm (range, 0.9–11.3 cm) at the time of presentation and 4.9 cm (range, 1.0–13.7 cm) at the time of last follow-up. The metastases were hypervascular on the post-contrast images and demonstrated linear enhancing intratumoral vessels (Figure 2).

Nodal metastases were seen in 17/23 (74%) patients. Hypervascular intrathoracic nodal metastasis was noted in 16/23 patients (70%), all of them having concurrent lung metastases. Of the 16 patients with primary tumour in the lower extremities, metastases to the locoregional nodes (inguinal) were noted in 4 patients. Supraclavicular (3/23, 13%), pelvic (3/23, 13%) and intra-abdominal adenopathy (2/23, 9%) were the other sites of nodal disease.

8 (62%) of the 13 patients with osseous metastases had a solitary bone lesion, whereas the remaining 5 patients had multiple lesions. Bone metastases were lytic in 11/13 patients (77%) (of which 5 were expansile), whereas 1 patient each had mixed lytic sclerotic and sclerotic metastases. Pathological fracture was noted in 3/13 patients and epidural soft tissue in 1/13 patients with bone metastases.

Brain metastases were seen in 10/23 patients, solitary in 4/10 and multiple in 6/10 patients. All the 10 patients had other sites of metastases at the time of diagnosis of brain metastases. The mean size of the brain metastases was 1.2 cm (range, 0.5–2.2 cm). With respect to location, 5/10 had isolated supratentorial, 2/10 had posterior fossa and 3/10 had both supratentorial and posterior fossa involvement. Solitary intraspinal metastasis was noted in one patient with both supratentorial and posterior fossa metastases. Brain metastases were intra-axial in 9/10 patients and extra-axial in 2/10 patients. Intra-axial metastases demonstrated homogeneous or peripheral rim-like enhancement and were associated with

Figure 2. Image of an 18-year-old male with ASPS metastatic to the lungs. Axial contrast-enhanced CT image of the chest shows bilateral hyperattenuating pulmonary metastases. The left lower lobe lesion shows linear enhancing intratumoral vessels (arrow).

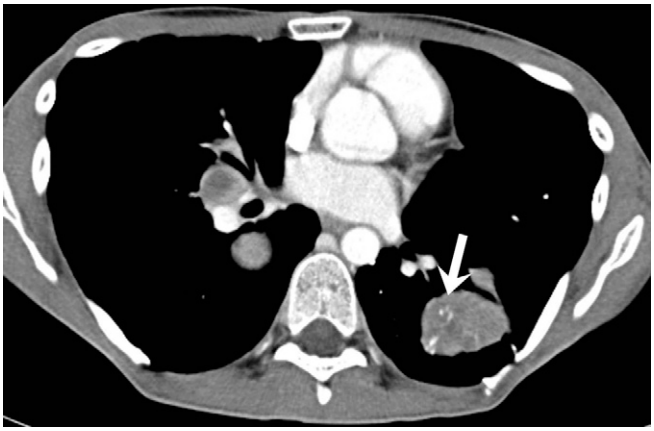
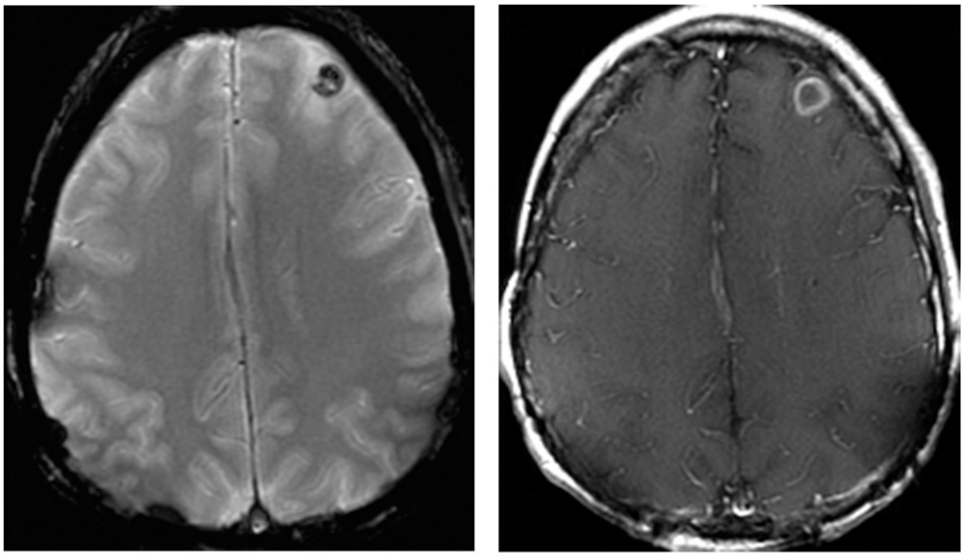


Figure 3. Images of a 27-year-old male with ASPS. (a, b) Axial gradient-weighted and post-gadolinium T_1 weighted images of the brain reveal a left frontal peripherally enhancing haemorrhagic metastasis with mild perilesional oedema and blooming artefact on the gradient-weighted image.



(a) (b)

perilesional oedema in four patients and haemorrhage in two patients (Figure 3). Extra-axial brain metastases were seen as a solitary leptomeningeal deposit in one patient and multiple focal epidural deposits in another patient.

Hepatic metastases were multiple in 7/8 patients and solitary in 1 patient. The hepatic metastases were all well defined and hypervascular, with a mean size of 4.7 cm (range, 1.4–10.3 cm). Adrenal metastases were noted in 8 patients; unilateral in 3/8 patients and bilateral in 5/8. Peritoneal sarcomatosis in the form of heterogeneously enhancing peritoneal implants was noted in five patients. Subcutaneous metastases were present in 6/23 patients (23%), with breast metastases present in 4 of them. Other sites of metastases included spleen (5/23), pancreas (3/23) and one each in the gall bladder, infratemporal fossa, muscle and kidneys. Pleural effusion was present in three patients.

PET/CT was performed in 8/23 patients, which demonstrated FDG-avid metastases in all of them. The FDG avidity was variable with a mean SUVmax of 6.7 (range, 2.9–9.2).

Management and outcome

Surgical resection of the primary tumour was performed in 21/25 patients with additional chemo/radiotherapy in 17 of them. Primary tumour was not resected in 3/25 patients, while the site of the primary tumour was unknown in 1/25 patient. The chemotherapeutic agents included doxorubicin, ifosfamide, cisplatin, carboplatin, cyclophosphamide and vincristine. Molecular targeted agents included bevacizumab, sunitinib and cediranib.

The median follow-up for all the 25 patients was 75 months (range, 12–180 months) during which 15/25 patients died, 6/25 are alive and 4/25 patients were lost to follow-up. The median time from the diagnosis of primary tumour to death in the 15 patients who are deceased was 72 months (range, 12–180 months). Of these 15 patients, the median survival was 74 months (range, 12–180 months) in the 8 patients who did not have brain metastases, in contrast to 60 months (range, 24–96 months) for the 7 patients who eventually developed brain metastases. The median interval between diagnosis of the primary tumour and the development of brain metastases was 38 months (range, 0–60 months), and the median time from development of brain metastases to death was 22 months (range, 7–56 months). Correlation of survival with the number of metastases at presentation showed that the median survival time was 128, 76 and 22 months for patients having no metastases, one site of metastatic disease and two or more sites at the time of presentation (ranges, 75–180, 24–146 and 12–24 months, respectively).

DISCUSSION

ASPS is a rare tumour with characteristic presentation and pathology. Its peak incidence is between 15 and 35 years, and it most commonly occurs in the extremities.[1,3,13] The findings in our study are in agreement with these earlier observations, with the mean age of presentation being 25 years and a majority (21–84%) of the patients presenting below 30 years. The age of presentation is younger than common sarcomas like gastrointestinal stromal tumor, liposarcoma and leiomyosarcoma which usually occur in the fourth to sixth decades.[14–16] There was a slight male predominance in our study (1.27:1), which contrasts with previous studies that have shown either no sex predilection or slight female predilection.[1,9,13] The extremities were the most common site of origin in our study (68%).

The imaging features of primary ASPS in our study were in agreement with earlier reports.[11,12,17] ASPS in our study was well circumscribed with lobulated contours and was isodense on CT and hyperintense on both T_1 and T_2 weighted images compared

with the skeletal muscles (Figure 1). All the tumours were hypervascular, demonstrating intense post-contrast enhancement and intratumoral flow voids. While the hyperintense signal on T_2 weighted images is related to the tumour cellularity the T_1 hyperintense signal in ASPS is hypothesized to be related to the slow flow in the intratumoral vessels.[11,12]

ASPS has a high propensity for haematogenous metastases. In a study of 74 patients by Portera et al,[1] 65% patients presented with metastases while in another study of 26 patients by Ogura et al,[9] 62% patients had metastatic disease at presentation. In our study, 18/25 (72%) patients had metastatic disease at the time of presentation, with 5 other patients developing metastases subsequently. The higher incidence of metastases encountered in our study is likely to be due to selection/referral bias and the use of modern imaging techniques compared with the above two studies, which included patients from 1959–1998 and 1979–2008 respectively.

In the 18 patients presenting with metastases, a single metastatic site (lungs in all cases) was present in 11 (61%) patients while the remaining 7/18 had more than one site of involvement. This is in agreement with the prior study by Portera et al,[1] who reported that 71% of the patients had a single site of metastasis at presentation. As is commonly seen in sarcomas, lung was the most common site of metastases in our study, being present in all 23 patients. This underscores the need to include thoracic imaging in the initial work-up of patients with ASPS. This is consistent with various other studies which also describe lung as the most common site of metastases (92–94%).[1,9] An interesting observation in our study was the presence of hyperattenuating lung metastases with intratumoral vessels, which is consistent with the hypervascular histology of ASPS (Figure 2). Similar findings were reported in a prior case series of three patients by Choi et al.[18] Nodal, abdominal visceral organ and peritoneal metastatic lesions were also hypervascular in our study.

ASPS has the highest incidence of brain metastases (19–30%) among all sarcomas.[1,19,20] The reason for this high incidence of brain metastases is unknown. In our series, 43% (10/23) of patients had brain metastases. Isolated brain metastases is however uncommon, with all the patients with brain metastases in our study having other sites of metastases. This concurs with the study by Portera et al,[1] who also demonstrated that isolated brain metastasis in the absence of extracranial disease is rare. Based on these observations, Portera et al[1] recommended that brain imaging can be limited to patients with other sites of metastases.

Imaging characteristics of central nervous system metastases in ASPS have not been well described in the literature. The appearance of the brain metastases in our study was not significantly different from that of other brain metastases. Brain metastases in our study were supra- and infratentorial as well as intra- and extra-axial with variable enhancement pattern, perilesional oedema (40%) and haemorrhage (20%) (Figure 3). Metastatic ASPS can be considered in the differential diagnosis for haemorrhagic intracranial metastases in a young patient in the appropriate clinical setting, along with other more common differentials like melanoma, lung, renal cell, thyroid and breast carcinomas and choriocarcinoma.[21,22]

Owing to haematogenous dissemination, nodal metastasis is uncommon in sarcomas. Some histological subtypes of sarcomas are, however, known to have a predilection for nodal metastases. Various studies have noted that clear cell sarcoma (11.1–38.0%), angiosarcoma (11.1–45.0%), epithelioid sarcoma (20–80%), ASPS (9.7–12.5%) and rhabdomyosarcoma (2.9–36.0%) have a high incidence of nodal metastases.[23–27] The incidence of nodal metastases in our study was 74%. The high incidence of intrathoracic lymph node metastases in our study has not been reported in ASPS previously and may in part be related to the high incidence of pulmonary metastases.

Data on the role of PET/CT in ASPS are scant with only a single case report to the best of our knowledge. Both the primary and metastatic ASPS in our study demonstrated variable FDG uptake, which is in agreement with the previously reported single case (SUVmax, 1.8–5.9).[28] The SUVmax values are also similar to other soft-tissue sarcomas. A review of 212 patients of sarcomas (both osseous and soft-tissue sarcomas) revealed the mean SUVmax value of the primary and/or the most avid metastatic lesion in the positive cases to range from 5.6 to 23.2 (median, 9.9), with most lesions having an SUVmax >2.5.[29] Another study of 109 patients revealed SUVmax of the primary tumour to range from 1.7 to 35.8 (median, 7.7).[30] The definite role of PET/CT needs further clarification but mainly lies in evaluating patients for metastases, for assessing response to treatment and in detecting recurrent disease.

Unlike other sarcomas, ASPS usually has an indolent course reflected by a median survival of 72 months in our study, despite the high incidence of metastases.[1] This observation is consistent with previous studies, which have described a median overall survival of 90–108 months, with a median survival of 40–41 months after the development of metastatic disease.[1,9] We also observed that brain metastases were associated with decreased survival, although this could not be statistically proved because of the small number of patients. Although the median survival was 74 months for those without brain metastases, it was 60 months for those who eventually developed brain metastases, indicating that the development of brain metastases in ASPS portends a poor prognosis. Furthermore, in the latter group, median time between diagnosis of the primary tumour and diagnosis of brain metastases was 38 months, whereas median time to death after the development of brain metastases was 22 months, indicating that the brain involvement might be responsible for the altered clinical course. Tumour burden at presentation also influences the survival, as patients with no metastases at presentation (median survival of 127.5 months) fared better than patients with single (median survival of 76 months) or multiple sites of metastases at presentation (median survival of 22 months). This necessitates proper staging at presentation to detect metastatic disease.

Limitations of our study include the retrospective study design and small sample size, especially the small number of patients with primary tumour imaging. The high incidence of metastases in our study is likely to be due to the referral bias in a tertiary cancer centre. Statistical analysis could not be performed owing

to the small number of patients, but this is unavoidable because of the rarity of the disease.

In conclusion, ASPS is a tumour of young adults and children often occurring in the lower extremities and having characteristic imaging features owing to its hypervascularity. It often metastasizes at presentation, frequently to the lungs, nodes, bones and brain and the metastases tend to be hypervascular. ASPS has an indolent course with long survival despite metastatic disease. Brain metastases and high tumour burden at presentation in terms of the number of metastatic sites were associated with shorter survival in our study.

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